KPFK

I am Linus Pauling, Professor of Chemistry in Stanford University. Today I shall talk about molecular diseases, diseases that have a molecular basis. In fact, I hope that I can talk about this general subject several times. I shall talk about some rare diseases and some common ones, later on even the common cold. I think that the common cold does not need to be so common as it is.

The human body is made up of molecules. And the _____ of disease are made up of molecules--the bacteria and viruses that produce the infectious diseases. In a sense, we might say that all diseases are molecular, that everything that happens to the human body has a molecular basis.

But there are certain diseases that have a specially close relationship to the molecules in the human body. In some of these diseases there are molecules present in the patients, the sufferers of the disease, that are closely similar to the molecules in ordinary human beings, but are not identical with them. They are abnormal molecules, we may say. In particular, some diseases are the result of the presence in the red ~~blood~~ cells of the blood of molecules of hemoglobin that are different from those that are present in the red cells of the blood of other people.

I have been interested in hemoglobin for nearly 40 years. In the early 1930's I began to think about the nature of hemoglobin and of other proteins in the human body. Hemoglobin is a protein, a substance containing nitrogen atoms which are present in amino acids. Hemoglobin molecules are made up of chains of amino acid residues. The hemoglobin molecule is a good molecule, containing four chains and about 300 amino acid residues altogether, about 150 or 140 in each of the four chains. This is rather new knowledge. It was not known in 1930 when I first became interested in hemoglobin. Hemoglobin is a beautiful substance, a red substance, which gives the color to the blood and the color to our skins in people who are not highly pigmented. The red color is, in fact,

the color of arterial blood, blood that has been oxygenated; the hemoglobin has combined with oxygen. The hemoglobin in the venous blood, the deoxygenated blood, is purply blue in color.

In 1936 Charles Coryell and I worked on the magnetic properties of hemoglobin. We found that a solution of hemoglobin itself is attracted by a magnate, whereas a solution of oxyhemoglobin is repelled by a magnate. That is, arterial blood is repelled by a magnate. And venous blood is attracted by a magnate. This was, for us, a very interesting experiment. Michael Farraday more than 130 years ago had tested the magnetic properties of old, ~~f~~ dried blood, and he made a ~~kn~~ note in his Diary that he should test recent, fluid blood. So far as I can find by reading his papers, however, he never got around to making this test.

The discovery of the interesting magnetic properties of hemoglobin afforded a method for determining a great number of properties of compounds of hemoglobin and the blood gave much information about the structure of the hemoglobin molecule, especially in the neighborhood of the iron atoms. Each hemoglobin molecule contains four atoms of iron, along with about 10,000 other atoms of carbon, nitrogen, oxygen and hydrogen. And it is to the iron atoms that the oxygen molecules attach themselves in the lungs.

As years went by, _____ and I continued to work on hemoglobin, determining the various properties of the substance. And then in 1945 I had a new idea: I was at a dinner with the other members of a committee on medical research _____ President Roosevelt in 1945. There were seven members of this committee. One of them, who is Professor in Harvard University, mentioned the disease sickle cell anemia. He said that the red cells of the blood are twisted out of shape in the patients with this disease--twisted into a sort of crescent shape or sickle shape. This is what caused Dr. _____ in Chicago, in 1910, to name the disease sickle cell anemia. These twisted red cells are recognized by the spleen as abnormal and are destroyed

by the spleen, causing the patient to become anemic. When he said that the red cells are twisted out of shape in the venous blood, and resume their normal shape in the arterial blood, that the disease--sickle cell anemia--is, in fact, a disease of the hemoglobin molecule. The difference between the arterial blood and the venous blood is that in the arterial blood the red cells contain oxyhemoglobin and in the venous blood hemoglobin. These molecules are somewhat different from one another because of the oxygen atoms attached to the iron atom. Ordinarily, nothing happens with respect to the shape of the red cell when the hemoglobin is oxygenated. If the hemoglobin were an abnormal hemoglobin, however, it might be a sort of supermolecule; such that, one molecule would stick to the next one and that to a third, producing a long rod, a clump, a linear clumping of the molecules. These long rods would then attract one another to make a long needle-like crystal, which, as it grew larger, could twist the red cell out of shape, causing it to be elongated.

When I returned to Pasadena, I found that a young physician, Dr. Harvey Itano, who had graduated in chemistry from the University of California, wanted to work with me for a Ph. D. degree. When I told him about the idea of studying the hemoglobin of patients with the disease sickle cell anemia, he decided to work on that project.

It was a hard problem and after a couple of years John Singer and Arthur Wells began to work with him. These three young men, Harvey Itano, John Singer, and Arthur Wells, succeeded then in showing that the hemoglobin in these patients is different from the hemoglobin in other people. A very small difference. Only two of the amino residues of the 280 are different. But that is enough to make the hemoglobin molecules thicker, and to produce the great deforming action on the red cells to make the patients anemic and to cause them to suffer from the disease.

This was the first time that a disease in a human being had been shown definitely to be the result of an abnormality in a molecule, of an abnormality in the hemoglobin molecule. It has been found now that there are many abnormal human hemoglobin molecules. Many diseases, similar to sickle cell anemia but not identical with it, have been discovered that are the result of the manufacture by the patient of abnormal forms of hemoglobin. This _____ of diseases is now called the set of hemoglobanemias, diseases of the hemoglobin molecules in the blood. About 100 abnormal human hemoglobins are known, and some abnormal hemoglobins _____ about a molecular basis of sickle cell anemia has led to significant progress in controlling the disease.

I think that the best way of controlling the disease is to prevent the children from being born. It is very easy to tell whether a man and his wife have a chance of producing a child with sickle cell anemia.

Professor Itano is now Professor in the Medical School in the University of California in San Diego and John Singer is Professor of Chemistry in the University of California, San Diego, Arnold Wells in State University of New York in Rochester. Dr. Itano, the first thing that he did when he came in 25 years ago to the California Institute of Technology to work with me, was to develop a simple test involving only a drop of blood, to tell whether or not a person carried the gene for sickle cell anemia.

About 10% of the people in certain areas in Sicily, Southern Italy, Greece, Northern Africa, Equatorial Africa, and other regions, and people in this country whose forebears came from these parts of the world, carry the gene for sickle cell anemia.

This disease is a genetic disease. The gene when present with a gene for normal hemoglobin produces a 50-50 mixture of normal hemoglobin and sickle cell anemia hemoglobin in the red cells. Fifty percent of the abnormal hemoglobin is not enough to cause the cells to sickle. But if two people carry a single sickle cell anemia gene plus a normal gene, marrying one another, then the probability that a child will inherit the abnormal hemoglobin gene from the father and the ½ abnormal hemoglobin gene from the mother, is 25 percent. On the average, a quarter of the children of the heterozygotes of the carriers of a single gene of sickle cell anemia are homozygotes with the gene in double dose--two genes of sickle cell anemia produce only the abnormal hemoglobin and their red cells sickle; they are the victims of a serious, hereditary disease.

A single drop of blood can be tested in a few minutes with a microscope and a little chemical reducing agent to see whether the cells sickle. If they sickle, and a person is not a sickle cell homozygote whose cells sickle very readily, then he can be identified as a heterozygote. If this test were carried out on every person, and the persons identified as heterozygotes refrained from marrying one another or having children, then there would be no children born with the serious disease sickle cell anemia.

I believe that this test ought to be carried out for every person. Every person should know whether or not he is a sickle cell heterozygote. And that such people should not marry one another. I think, moreover, that they should have a smaller than average number of children when they marry a person who does not have the sickle cell disease. If they restricted themselves to one child or two children, then in the course of time the sickle cell gene would die out.

There are several interesting aspects of this story. We may ask why it is that in certain parts of the world the incidence of the sickle cell gene in the population is very high. In some parts of Africa and around the Mediterranean area, Eastern Mediterranean area, the incidence is as high as 50 percent.

The answer to this question has been discovered. It has been found that having a sickle cell gene provides protection against malaria. The malaria parasite lives inside the red cell and eats the hemoglobin. The abnormal hemoglobin, for some reason, does not agree with him. These parasites do not develop in the cells with abnormal hemoglobin and, accordingly, the heterozygotes and presumably the homozygotes in the sickle cell gene _____ to prevent anemia.

You can understand what happened, perhaps 10,000 years ago in a village where the people were ravaged by malaria, which is, I think, a rather young disease. It is, perhaps, only 10,000 years old. A cosmic ray or other mutagenic agent produced a gene mutation, such that the person manufactured sickle cell xxxxxxxxxx hemoglobin as well as normal hemoglobin. He was protected against anemia. Half of his children, when he married another person, would inherit the sickle cell gene and be protected against anemia. They would survive when the other persons died. And so the sickle cell would spread rapidly through the population. Perhaps in a 1,000 years it had spread very widely through that part of the world. Then, as the heterozygotes married one another, a quarter of their children would inherit the two normal hemoglobin genes and would die of malaria. A quarter of them would inherit the two sickle cell anemia genes and would die of sickle cell anemia. But half of them would be heterozygotes, ~~like~~ as their parents. They would not have a serious disease, because their cells do not sickle with only 50 percent of the sickle cell hemoglobin; thus, they would be protected against malaria.

This is a step in evolution. An evolutionary step that is x of such a nature as to provide protection against a serious disease--malaria.

The next step that might well have taken place with a little longer time, during which people were subjected to malaria, would be another mutation that produced a form of hemoglobin that provided protection against malaria, when the gene was present in the double dose, and that did not produce the sickling of the red cells. Now that malaria is controlled pretty well by the elimination of mosquitoes and by the use of antimalarial drugs, we can be reasonably sure that this next step will not take place, unless, of course, there is the catastrophe of a nuclear war, civilization is destroyed, the remnants of the human race who remain revert to a primitive state, then the processes of evolution may begin to operate again, with respect to hemoglobin and malaria and we may be back in the stone age again, without means of preventing mosquitoes from infesting the countryside and without means of synthesizing the antimalarial drugs.

The process of evolution from the molecular point of view has been illuminated during recent years by the study of the hemoglobin. One of the persons who carried out studies of the hemoglobin of man and various animals is Dr. Emile Zuckerkandl, who worked with me for five years in Pasadena, and has been now for nearly a decade as the chief of a scientific laboratory in the south of France, in Montpellier, France. Dr. Zuckerkandl studied the hemoglobins of human beings and of horses, cows, dogs, pigs and other animals, and the gorilla, the orangutang, the chimpanzee, and fish, and other species of animals that have hemoglobin in their red cells.

Other people, for example Professor Emile Smith, in the University of California in Los Angeles, have also made similar studies. The results of these studies are, I think, very interesting. It was found that the hemoglobin of man consists of two chains--the beta chain, each of which contains 141 amino acid residues, and two, the alpha chains, containing 146 residues a piece.

Horse hemoglobin differs from human hemoglobin in about 18 residues in each of these chains: the alpha chain and the beta chain. Eighteen out of 140, 141 and 146. This is about a seventh of the residues. The other residues, about 125 residues, are identical. In each position the same one of the 20 different amino ~~acids~~ acids, lycine, alamine, phenylalamine, and so on, appears in horse hemoglobin and human hemoglobin.

Now anthropologists and geologists tell us that the strains--the lines of evolution leading to present-day horse and present-day man--separated about 70 million years ago. This would mean that one evolutionarily effective mutation had occurred in the gene for the beta chain of hemoglobin every 4 million years on the average, in either horse or man. And similarly, one evolutionarily effective mutation every 4 million years in the gene for the alpha chain in horse or man. Every eight million years in the horse. Every eight million years in man.

When we looked at _____ hemoglobin, rhesus monkey hemoglobin, it turned out that the alpha chain and the beta chain are much more similar to the human alpha and beta chain. Only 6 residues in the alpha chain of the monkey are different than those in the human being. And only 6 in the beta chain. This means, when we multiply by 4 million years, that we can conclude that about 24 million years ago the lines of evolution leading to present-day monkey and present-day human beings separated from one another. This is not an unreasonable estimate according to the paleontologists, and it is independent of the anthropological studies; but, of course, it is based on the assumption that it is 70 million years ago that horse and man separated from one another.

The gorilla beta chain differs from human beta chain in only one residue. For gorilla, orangutan, and chimpanzee, the alpha chains and beta chains differ from human alpha and beta chains in one residue or two residues only out of 141 or 146. The difference in the hemoglobins of human beings and the gorilla, orangutan, and chimpanzee, is less than 1 percent of the amino acid composition. Multiplying by 4 million years, we conclude that the lines leading to present-day human beings and present-day gorilla, orangutan, and chimpanzee, separated from one another somewhere around 6 million years ago. One residue corresponds to 4 million years, two to eight million years.

This is, of course, reasonable. Evidence for ailing man goes back to a period a million to two million years ago., perhaps one and one-half million years ago, and to an earlier time, which the hemoglobin molecule suggests to be about 6 million years ago, the lines diverged from one another. The mutations took place that caused a large increase in the size of the brain. The process of abstract thinking and the development of speech occurred and man started on what we might call his modern period.

I shall talk more, later on, about the molecular basis of disease.

Thank you.